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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/935,316 | 08/22/2001 | Ching-Leou Teng | ISIS-4824 | 1463 |

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| EXAMINER | |
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 03/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/935,316 | TENG ET AL. | |
| | Examiner | Art Unit | |
| | Jon Eric Angell | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *28-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This Action is in response to the communication filed on 1/03/05. The amendment filed 1/3/05 is acknowledged. The amendment has been entered. Claims 28-39 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

### *Claim Rejections - 35 USC § 112, 2nd paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the actual methods steps that are required to activate the intestinal tissue. As written, the claims are merely a preamble, "a method for enhancing intestinal absorption of a drug" and a desired result of the method, "activating the intestinal tissue with a penetration enhancer prior to allowing a drug to interact with said intestinal tissue." There are no specific method steps that indicate how to activate the intestinal tissue with a penetration enhancer prior to allowing a drug to interact with said intestinal tissue. Therefore the instant claims do not indicate a complete method. Claim 29 is dependent on claim 28 and is rejected for the same reasons.

***Claim Rejections - 35 USC § 102***

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 28-36, 38 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 5,877,309 (McKay et al.)

The instant claims are drawn to:

A method for enhancing intestinal absorption of a drug comprising activating the intestinal tissue with a penetration enhancer prior to allowing a drug to interact with said intestinal tissue (claim 26); wherein the drug is formulated with a bioadhesive (claim 27); and,

A method for enhancing the intestinal absorption of a drug in an animal, said method comprising administering to the animal:

(a) a first population of carrier particles comprising a drug-bioadhesive component; and,

(b) a second population of carrier particles comprising a penetration enhancer,

wherein upon entry in to the intestine, said penetration enhancer is released and move down said intestine while acting on a mucosal membrane of said intestine, and said drug-bioadhesive component adheres to said mucosal membrane and releases said drug directly to said mucosal membrane that is activated by said penetration enhancer, whereby intestinal absorption of said drug is enhanced (claim 30); wherein the first

population is prepared as a tablet or a multiparticulate formulation (claim 31); wherein the second population is prepared as a tablet, multiparticulate, emulsion microemulsion, or self-emulsifying system (claim 32); wherein the drug is an oligonucleotide (claim 33); wherein the penetration enhancer is a fatty acid (claim 34); wherein a bioadhesive of the drug-bioadhesive is a polyacrylic polymer (claim 35); and wherein the oligonucleotide is an antisense oligonucleotide (claim 36); wherein the bioadhesive comprises a polyacrylic polymer (claim 38); wherein the bioadhesive further comprises a hydroxypropyl-methylcellulose (HPMC) (claim 39).

McKay teaches a method which comprises administering to a human a composition comprising a drug that is an antisense oligonucleotide (e.g., column 6, lines 29-65); wherein the antisense oligonucleotide is comprised in a formulation for oral delivery which can comprise a polyacrylic polymer, such as capric acid and polyacrylates (e.g., see: col. 20, lines 52-54; col.22, lines 4-19; col. 23, lines 24-40; col. 25, lines 1-7; and col. 28, lines 3-4). McKay teaches that the therapeutic formulation can be comprised in a tablet (e.g., see column 22, lines 67). Furthermore, McKay teaches that the antisense drug composition can comprise hydroxypropylmethylcellulose and polyacrylates (e.g., see col. 23, lines 29-40).

Therefore, McKay teaches a method comprising administering to a subject a composition comprising all of structural elements of instant claims. Therefore, the method taught by McKay, absent evidence to the contrary, would necessarily result in the penetration enhancer, upon entry in to the intestine, being released and moving down the intestine while acting on a mucosal membrane of the intestine; as well as the drug and bioadhesive component adhering to the

mucosal membrane and releasing the drug directly to the mucosal membrane that is activated by the penetration enhancer, resulting in enhanced intestinal absorption of the antisense drug.

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 30, 33 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,877,309 (McKay et al.), further in view of US Patent 5,514,788 (Bennett et al.).

It is noted that McKay teaches a method for enhancing the intestinal absorption of an antisense drug in an animal, comprising administering to the animal a formulation comprising: (a) a first population of carrier particles comprising an drug-bioadhesive component, wherein the drug is an antisense oligonucleotide; and (b) a second population of carrier particles comprising a penetration enhancer, as indicated above.

McKay does not teach that the oligonucleotide comprises SEQ ID NO: 1 (claim 37).

However, Bennett teaches an antisense oligonucleotide that exactly matches SEQ ID NO: 1 of the instant claims (see SEQ ID NO: 22 in column 35 of Bennett) wherein the antisense oligonucleotide can be used administered to an animal for a method of treatment (e.g., see abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of McKay and Bennet to make a method comprising administering to an animal a composition comprising (a) a first population of carrier particles comprising an drug-bioadhesive component, wherein the drug is an antisense oligonucleotide comprising the antisense oligonucleotide taught by Bennet; and (b) a second population of carrier particles comprising a penetration enhancer, with a reasonable expectation of success.

The motivation to make the modification is provide in part by both McKay and Bennett. Specifically, McKay teaches a method for administering a therapeutic antisense oligonucleotide to an animal and Bennett teaches a specific therapeutic antisense oligonucleotide comprising SEQ ID NO: 1.

***Response to Arguments***

Applicant's arguments filed 1/3/05 have been fully considered but they are not persuasive.

Applicants assert that the new claims are not anticipated by the 309 patent (McKay) because the new claims clarify that the method of enhancing the absorption of a drug entails

activating the intestinal tissue with a penetrating enhancer prior to allowing a drug to interact with said intestinal tissue and the prior activation may be achieved through administering two separate population of carrier particles (e.g., a first population of carrier particles and a second population of carrier particles). Furthermore, Applicants assert that the first population and second population are separate in that the first population may be prepared as a tablet or a multiparticulate formulation, and the second population may be prepared as a separate tablet, multiparticulate, emulsion, microemulsion or self-emulsifying system. Applicants acknowledge that the 309 patent (McKay) teaches a mixture comprising a polyacrylate (a bioadhesive) (col. 23, ln. 39) and a capric acid (a penetration enhancer) (col. 22, ln. 17). However, Applicants assert that the 309 patent (McKay) fails to teach that the polyacrylate is part of the first population of carrier particles comprising a drug-bioadhesive component, and that the capric acid is part of separate/different second population of carrier particles. Applicants also assert that the 309 patent does not disclose that the first population may be prepared as a tablet or a multiparticulate formulation, and the second population may be prepared as a separate tablet, multiparticulate, emulsion, microemulsion or self-emulsifying system (see p. 4-5 of the response filed 1/3/05).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the first population comprising a drug-bioadhesive component and the second population comprising a penetration enhancer can be present in separate compositions) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the

specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants appear to be arguing that the references do not teach that the two populations of carrier particles can be comprised in separate compositions, such as separate tablets. It is noted that the claims do not specifically claim that the two populations are in separate compositions. Rather the claims encompass a single composition comprising both the first and second populations together in a single composition, such as a tablet. Furthermore, the specification specifically indicates that,

> "Preferably, the carrier particles are incorporated into an oral dosage form. In another aspect of this preferred embodiment, the oral dosage form is a tablet, capsule or gelcap... the first and second population of carrier particles are administered in a single dosage form." (See the last three lines of p. 3 through the first paragraph on p. 4 of the specification); and,
>
> "The first and second populations of carrier particles may be formulated separately or, preferably, incorporated into the same pharmaceutical formulation... The two types of carrier particles are then formulated separately or together into oral dosage formulations such as tablets, capsules or gelcaps..." (See paragraph 17, p. 7).

Therefore, in addition to the lack of a specific limitation in the claims that the two populations are in different/separate compositions, the specification clearly contemplates (and even indicates that it is preferable to administer the two populations in a single dosage form, such as a tablet.

Therefore, Applicants arguments are not persuasive and the instant rejections are proper.

***Conclusion***

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell, Ph.D.
Art Unit 1635

DAVE TRONG NGUYEN
PRIMARY EXAMINER